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ENLARGED THYROIDS IN UNIVERSITY OF CALIFORNIA WOMEN STUDENTS

STUDIES IN INCIDENCE AS RELATED TO RESIDENCE

By RUBY CUNNINGHAM *

An editorial adviser who evaluated Doctor Cunningham's paper for the editor says: "I feel that the paper has statistical value not only for physicians in California, but also for those seeking data on the incidence of thyroid enlargements on the Pacific Coast.

DISCUSSION *by H. Lisser, San Francisco; E. H. Risley, Loma Linda.*

AMONG 7320 women students entering the University of California during the last five years 1361, or 18.6 per cent, had enlargement of the thyroid gland. The percentage has varied somewhat from year to year, depending upon the enthusiasm and skill of the examiners and their judgment as to where enlargement becomes pathological.

The physical examination required of freshmen is a hurried one. Students found to have physical defects are given a reappointment card so that they may be more carefully studied at a later date. During the last few years special attention has been given to students with enlarged thyroid glands. They have been asked to fill out a questionnaire, which calls for the birth places of themselves and their mothers, their various residences, and other facts of their history not included in routine histories. Almost all students who return for a re-examination of the thyroid were seen by a group of physicians from the University of California Medical School experienced in the recognition of thyroid disturbances; frequently the diagnosis was the result of a consultation.

Five hundred students with enlarged thyroids have been carefully studied in this way. They were taken in order of their entrance to the university and unselected except for the fact that students with small thyroids due to adolescence were not all included. The enlargement in 250 of the 500 patients was due to simple goiter of the adolescent type. Seventeen were of the adolescent type with beginning colloid changes and thirty-eight were typical colloid glands. One hundred and sixty-one had adenomata. In 147 the tumor appeared in glands otherwise normal, and in fourteen in colloid glands. One hundred and forty-three adenomata seemed nontoxic and where tested the metabolic rate was normal; eighteen remaining adenomata were toxic and were responsible for metabolic rates above normal. Thirty-four had hyperplastic enlargements with symptoms of hyperthyroidism. A report of the symptomatology and physical findings in this group is in progress.

Of the 500 students thus studied, 337 were born in other countries or states and 237, or 47 per cent, spent their childhood and adolescence outside of California. This means that California is wholly or in part responsible for only slightly more than half of the enlarged thyroids on its college campus.

The known goiter areas of the United States furnished a considerable number of the out of the state students with abnormal thyroids; seventy-three had spent all of their lives in one of the states bordering on the Great Lakes and forty-one in a state of the northwest goiter area. Sixty-three had spent all of their lives in one or more of the lake states and some had migrated to western goiter areas. Thus 177, or 74 per cent, of the students coming from other states with abnormal thyroids had resided in states or countries in which the goiter incidence is high.

A westward migration of those with or who later developed enlarged thyroids is indicated by a study of the birth places of patients and their mothers and the residences of the patients in childhood and adolescence. The incidence decreases from mother's birth place to the patient's residences during adolescence in eastern states with corresponding increases in populations in western states. Some of these conclusions are supported by the following table:

WESTWARD MIGRATION OF THOSE WITH ENLARGED THYROIDS

	California	Wash., Ore., Utah, Idaho	Great Lakes States
Mother's birth place....	86	23	216
Student's birth place....	116	60	173
Childhood residence.....	205	77	148
Adolescence residence	263	63	112

Doubtless, elsewhere in the west the incidence of enlarged thyroid is increased as it is among the University of California students by westward migration.

Of 2341 students registering from California 245, or 10.5 per cent, showed thyroid enlargement. Since the state possesses a wide range of geographic, geological and climatic conditions, we may expect the

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incidence of enlarged thyroids to vary in different sections. This is confirmed by the following table:

THYROID INCIDENCE IN CALIFORNIA BY GROUPS OF COUNTIES

	Residence of 2341 recent entrants	Residence of those with enlarged thyroids among the 2341	Per cent thyroids enlarged	Number with enlarged thyroids spending their lifetime in the county
Volcanic Regions:				
Siskiyou, Modoc, Lassen counties	18	8	44.4	7
Mountain Counties:				
Trinity, Shasta, Tehama, Plumas, Placer, Sierra Nevada, Alpine Eldorado, Amador, Calaveras, Mariposa, Tuolumne, Mono, Inyo	65	16	24.6	10
Coast Range Counties:				
Del Norte, Humboldt, Mendocino, Sonoma, Lake, Marin, Solano, Napa, Contra Costa, Santa Cruz, Santa Clara, Monterey, San Benito, San Luis Obispo	279	60	21.5	30
So. California Counties:				
Santa Barbara, Ventura, Los Angeles, Orange, Riverside, San Bernardino, San Diego, Imperial	313	58	18.5	10
Valley Counties:				
Butte, Glenn, Colusa, Sutter, Yolo, Yuba, Sacramento, San Joaquin, Stanislaus, Merced, Fresno, Tulare, Kings, Kern	295	27	9.1	13
Bay Counties:				
San Francisco, San Mateo, Alameda	1372	76	5.5	22

The mountainous volcanic area in the northeast corner of the state sends few students to the university, but of this number 44.4 per cent have enlarged thyroids. Seven of the eight students with enlarged thyroids were born and brought up in the county from which they registered, so the locality may be considered intimately associated with their goiters. Goiter of adolescents, often spoken of as mountain goiter, may explain why the Sierra Nevada mountain regions of California furnished a high percentage, 24.6 among our students. Insufficient iodin intake is no doubt the chief factor in the production of mountain goiter. A high incidence of enlarged thyroids has long been noted in limestone regions, and animal experiments have shown iodin to be less effective in protecting against thyroid enlargement where associated with lime salts. The limestone belt, which runs from Mariposa County to Tehama County through the lower slopes of the Sierra Nevada, may be a factor in this moderately high incidence of enlarged thyroids, but as it occurs below the cities of gold-mining origin and above the farming belt and is sparsely settled, it can only affect a very limited number of individuals.

The Coast Range mountain counties are a close second to the counties of the high mountains with a 21.5 per cent production of enlarged thyroids. Here the limestone deposits may be a considerable factor since they are more widespread and some in well-populated areas. The elevation, which is probably associated with water supplies poor in iodin, is no doubt the chief causative factor. The population in these counties is moderately stationary, as indicated by the fact that one-half of those with enlarged glands had spent their entire lives in one county. The counties of the great valley show a 9.1 per cent incidence of goiter among the young women who come from them to the university. Unfortunately for the accuracy of our deductions, many of these counties have mountainous parts. Some of the six patients from Butte County and some of the eight from Fresno County may have come from mountainous parts of those counties. Girls from counties which are entirely upon the floor of the valley have a very low thyroid incidence.

The fact that only ten of the fifty-eight patients with enlarged thyroids grew up in southern California may indicate that the apparent incidence of 18.5 per cent is also influenced by nonresidents from goiter zones.

About the San Francisco bay we find few enlarged thyroids—5.5 per cent. Here our figures are the most reliable because they are the largest. The rather striking differences between the percentages for San Francisco County on the coast side (10.8 per cent) and Alameda County on the inland side of the bay (3.2 per cent) are interesting, especially when we note that seventeen of the San Francisco students and only four of the east bay region students grew up in their respective counties. This may be a prediction as to the iodin content of the water supplies of the two counties.

DISCUSSION

H. Lisser, M. D. (384 Post Street, San Francisco)—Each new statistical study of goiter incidence, if completely performed and wisely interpreted, constitutes a valuable contribution to our knowledge of the geographical distribution of so-called endemic goiter. Doctor Cunningham's paper affords an excellent example of this sort of investigation. Such goiter surveys are an essential prelude to any intelligent and comprehensive campaign for prophylaxis.

The ordinary "simple," "adolescent," "puberty," "endemic" or "diffuse colloid goiter" is but rarely associated with any marked derangement of thyroid function; at least not for several years after its appearance; a mild hypothyroidism may accompany the goiter, but usually escapes detection, and an associated autonomic imbalance is apt to be confused with Graves' disease. But the vast rank and file of adolescent goiters cause no disturbance other than a cosmetic embarrassment, and may even add beauty to the neck by rounding out its contours. Their significance consists in their potential danger for the future. Just as syphilis may appear to slumber innocently for ten or thirty years only to create havoc in later life, so the apparently harmless goiter may persist for a similar period, becoming adenomatous the while, and toxic later on.

It is therefore interesting to note that 161 of the 500 goiters reported by Doctor Cunningham contained adenomata already, and that eighteen of these gave evidence of toxicity. It would be even more interesting to have a second report ten years from now and a third report in twenty years in the nature of a "follow-up" in order to ascertain how many of the at present "adenomatous goiters *without* hyperthyroidism" had changed their character into "adenomatous goiters *with* hyperthyroidism." And it would be equally enlightening to learn how many of the simple goiters without adenomata had developed adenomata in the next ten years. Our therapeutic advice hinges largely on such data. There is no justification in our recommending surgical extirpation of adenomatous goiters which are causing neither regional pressure symptoms nor constitutional hormonic disturbance, unless adequate and accurate statistical data prove convincingly that a large percentage of these adenomata become toxic after 40 years of age. This is the contention of the Mayo

Clinic, and the converted disease is sometimes referred to as Plummer's disease.

The practical clinical import of Doctor Cunningham's statistics lies in the recognition of three prophylactic periods: (1) the prepubescent period, with prophylactic administration of iodin in areas where goiter is endemic; (2) the adolescent age, with the prompt administration of iodin before the goiter has become adenomatous and refractory to iodin; and (3) the early adult period, with the prophylactic removal of adenomata in order to prevent subsequent damage to the myocardium and the nervous system. Widespread goiter prophylaxis on a huge scale may prove to be as brilliant a public health measure as the campaigns for the eradication of typhoid, malaria, and yellow fever.

E. H. RISLEY, M. D. (College of Medical Evangelists, Loma Linda, California)—Doctor Cunningham's paper is a most interesting and valuable contribution to our knowledge of goiter. This is especially true since it applies in a special way to the state of California. Such studies are all the more important on account of the fact that they deal with a problem which can be benefitted by prophylactic measures.

The fact that 18.6 per cent of the young women, the very flower of the flock, in one of the leading educational institutions in the state show a disturbance of this kind should be a warning to us to be in earnest about applying measures for the relief of the situation.

It is true, as Doctor Lisser says, that many of these young women will never have serious trouble, but the potentialities are there and no one can predict who the victim will be.

McClendon and others have pointed out the etiologic relation of low iodin content of food and water to the incidence of goiter, and it seems that the statistics collected in this paper tend to prove the same idea, since in California surface water is generally low in iodin and well water often rich, it would seem plausible that the different localities mentioned might vary in the frequency of goiter manifestations as the iodin content of food and water varies. It would seem that a further correlation of Doctor Cunningham's findings might be exceedingly helpful.

One of the very practical values of this paper lies in the impetus it gives to the profession to help in educating the laity in regard to nutritional problems so as to avoid the serious consequences which may follow deficiency in diet.

THE BASIC CONCEPTS OF IMMUNITY *

By W. H. MANWARING

(Jour. Immunol. 12 (3): 177-84, 1926)

An inquiry as to whether or not the three major hypotheses underlying the Ehrlich theory as to the origin and nature of antibodies are in accord with known physiological facts. The paper cites a dozen or more physiological facts drawn from blood transfusion, organ transplantation, and perfusion experiments that are inconsistent with the Ehrlich hypotheses. Many of the facts are even wholly unthinkable from the Ehrlich point of view. The conclusion is drawn that the Ehrlich theory is merely of historical interest, that it should be discarded by practical serologists and clinicians, and eliminated from elementary textbooks for medical students.

As a substitute for the Ehrlich theory, the author suggests the theory that immunological antibodies are not hypertrophied, desquamated, pre-existing protoplasmic fragments ("side-chains") as the Ehrlich theory assumes, but that they are new substances, formed as a result of interaction between injected antigens and extracellular and intracellular hydrolyzing and synthesizing enzymes, and by these enzymes specifically adapted to the antigens or to products of antigen hydrolysis. The author believes this theory is in accord with the known facts of cellular biology, and that its acceptance would stimulate the hope that in time therapeutic antibodies, possibly even superior to those formed in the animal body, may be successfully synthesized in the chemical laboratory.

* Presidental Address, American Association Immunologists, Albany, New York, April 1, 1926.

MODERN MANAGEMENT OF EXOPHTHALMIC GOITER †

(From the Division of Surgery, Mayo Clinic, Rochester, Minnesota)

By JOHN DEJ. PEMBERTON *

EXOPHTHALMIC goiter was first described as an entity in 1825 by Parry, who published an account of eight cases. Later, Graves in 1835, and von Basedow in 1840 described the clinical findings. Curiously, not until the eighties was it accidentally discovered by several surgeons, Tillaux, Rehn, and Mikulicz, that the disease could be cured by operation on the thyroid gland. Since then surgery has made stupendous strides, holding an increasingly dominant rôle in the treatment of this malady, although history bears ample testimony that the path of progress of surgical treatment of the thyroid has been difficult and beset with many obstacles.

While the cause of exophthalmic goiter is not known, and is in all probability not thyrogenic, there is consistently a characteristic pathologic picture of diffuse, parenchymatous hypertrophy and hyperplasia in the thyroid gland, and, moreover, the successful resection of the gland is invariably followed by immediate remission of symptoms. All evidence points to the fact that the gland is delivering to the body an excessive amount of secretion, probably altered or perverted in character. As no substance has been found which will neutralize or counteract the action of the secretion in the tissues, practically all successful methods of treatment have aimed to diminish the activity of the gland by interference with its blood, lymph or nerve supply, or by partial destruction of the gland by resection, injections, or irradiation. As the preservation of a functioning portion of the thyroid gland is necessary for the maintenance of health, the important desideratum in any method employed should be reduction of hyperactivity without loss of function.

It was soon recognized that surgery offered means of removing excessive thyroid tissue, and at the same time insured the preservation of sufficient tissue for the maintenance of health. However, in the pioneer days surgical resection of the gland was attended by an almost prohibitive mortality and morbidity. A mortality of 25 per cent or even higher was not uncommon, and obstructive dyspnea, tetany, and myxedema were frequent postoperative sequelae. Many factors were responsible for these results, chiefly the faulty operative technique and lack of knowledge of the natural course of the disease. Frequently patients died even after an uncomplicated operative procedure, the result of crisis. It is not surprising therefore that with such a discouraging mortality only a few men ventured to develop this field of surgery. However, the very striking and obvious improvement in the patient's condition fol-

† Read before the California Medical Association in General Session, Oakland, 1926.

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